



7

Lys Val GGA **1**33 크 Phe Leu AAT Leu AAT Leu GAG Leu Ala CG CIGGAC Leu TAA TGA 크

₩ E

AGG TAC ACG 286 ACC 1GG

Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 10/076,604

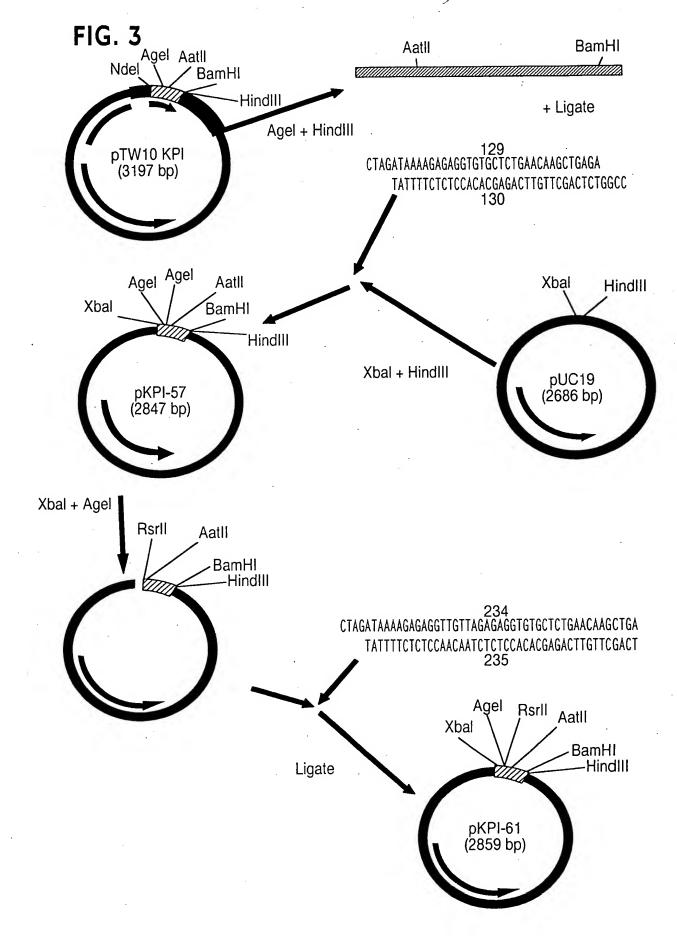
Aatll

AAA TTC CGA 길 8 AAA TAC

RamH Hindl

TAA CGA AGG GGA CAC a AAC







Rsrl

Agel GAG

)))) CCA CIC

AGA

GAG

AAA

Val

Asp

CGA AAG TGA GAC AAA ACC AGG

TAG

TAC

GCA CGT

Title: PROTEASE INHIBITOR **PEPTIDES** Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

> SGI Ser Met

GAG CTC Glu GAA CTG GAC AAA AAC TTG AAC TTG AAC TTG 999 999 299 TGC ACG ATG AAA AAG

ATT TAA GCT CGA TCC GGA TGC ACG TAC TAC



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

TGC ACG Oys

ACC GAG CAA GAA

GTG

GAG

AGA .

GII

AAA

CAA

Val

CIC GTT

<u>_</u> AGA Ser ACG SS CAC Val

GAC

ATG TAC

360

TGA CIGAAA ATG TCC

CTG AAA TTGTTG GCA TTG 900 ACG GGT CCA ATG

GAA CITT Glu

TGA

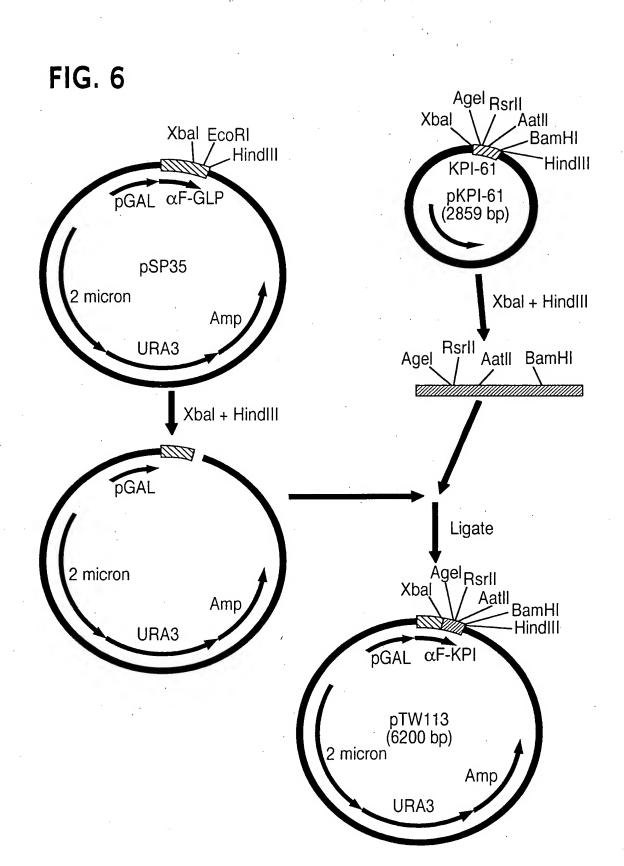
AAG

Hind|| TA ATT (ATT TAA 11e GCT CGA TCC GGA TGC GTG



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 7

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT
Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC TAG AGG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Met Ile Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

Aatll

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



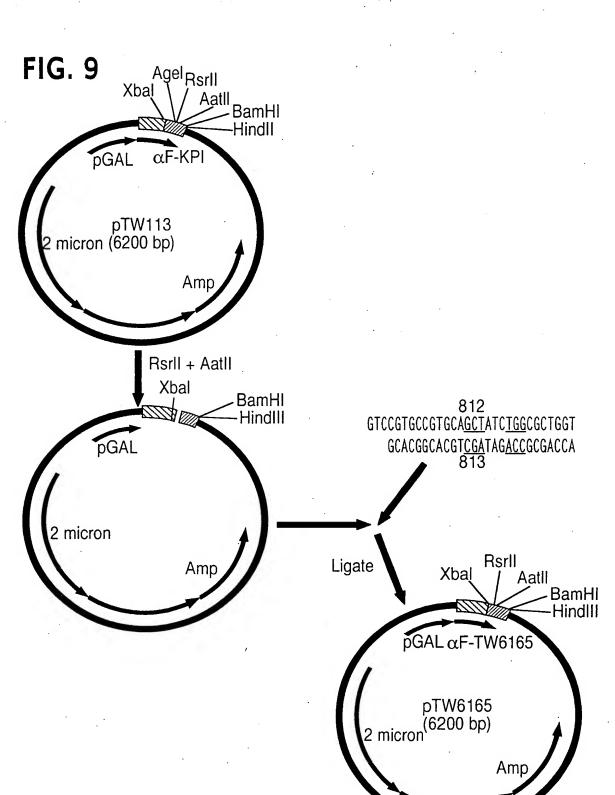
Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 8

KPI(-4-57) Glu - Val - Val - Arg - Glu - Val - Cys - Ser - Glu - Gln - Ala 2 · 3 5 -2 -1 1 4 -4 -3 Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met - Ile - Ser - Arg 8 9 10 11 12 13 14 15 16 17 18 Trp - Tyr - Phe - Asp - Val - Thr - Glu - Gly - Lys - Cys - Ala 25 21 22 23 24 26 27 28 19 20 Pro - Phe - Phe - Tyr - Gly - Gly - Cys - Gly - Gly - Asn - Arg 32 33 34 35 36 37 38 31 40 Asn - Asn - Phe - Asp - Thr - Glu - Glu - Tyr - Cys - Met - Ala 41 42 44 .45 46 47⁻ 48 49 50 51 43 Val - Cys - Gly - Ser - Ala - Ile 55 52 53 54 56 57





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Title: PROTEASE INHIBITOR
PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 10

pTW 6165

α-factor

ATG AGA TIT CCT TCA ATT TIT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT

Ser Thr Asn Asn Gly Leu Leu Phe ile Asn Thr Thr ile Ala Ser ile Ala Ala Lys

Xbal

KPI(-4-57; M15A, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU Val Ser Leu Asp Lys Arg Giu Val Val Arg Giu Val Cys Ser Giu Gin

RsrII -

Agel

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TGG CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ACC GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG
Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

Hindill

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Title: PROTEASE INHIBITOR
PEPTIDES
Inventor(s): R. Tyler WHITE et al.
Appl. No.: 10/076,604

FIG. 11

FIG. 11	
812 GTCCGTCCCGTCCACCTATCTCGCCCTCGTACTTTCACGT CCACCGCACCG	pTW6165 KPI(-4-57; M15A, S17F)
814 GTCCGTCCCGTCCACCTATCTACCCCTCGTACTTTCACGT CCACCGCACCG	pTW6166 KPI(-4-57; M15A, S17Y)
867 GTCCGTCCCGTCCATTCATCTTCCCCTCGTACTTTCACGT CCACCGCACGTAACTACAACGCCACCATCAAAC 868	pTW6175 KPI(-4-57; M15L, S17F)
1493 GTCCGTCCCGTCCA <u>TTC</u> ATC <u>TAC</u> CCCTCGTACTTTCACGT CCACCGCACCGT <u>AAC</u> TAC <u>ATC</u> CCCACCATCAAAC 1494	pBG028 KPI(-4-57; M15L, S17Y)
925 GTCCGTCCCATCCACTTCCCCTCGTACTTTCACGT CCACCGCACGTTACCGTCAACGCCCATCAAAC 926	pTW6183 KPI(-4-57; I16H, S17F)
927 GTCOGTCCCATCCACTACCCCTCGTACTTTCACCT CCACCCCACGTTAC <u>GTCATC</u> CCCACCATCAAAC 928	pTW6184 KPI(-4-57; I16H, S17Y)
929 GTOOGTGOOGTGCAATG <u>CACTGG</u> OGCTGGTACTTTGAOGT GCACGCCACGTTAC <u>GTGACO</u> GOCACCATGAAAC 930	pTW6185 KPI(-4-57; I16H, S17W)
863 GTCOGTGCCAGCTCACTCCCCCTGGTACTTTGACGT GCACGCACGT <u>CGAGTG</u> ACGGCCACCATGAAAC 864	pTW6173 KPI(-4-57; M15A, I16H)
865 GTOOGTGOOGTGCA <u>TTGCAC</u> TOOOGCTGGTACTTTGACGT GCACGGCACGT <u>AACGTG</u> AGGGOCACCATGAAAC 866	pTW6174 KPI(-4-57; M15L, I16H)

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Title: PROTEASE INHIBITOR PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 12

pTW 6166

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln IIe Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57; M15A, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Giu Val Val Arg Giu Val Cys Ser Giu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 13

pTW-6175

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG IIIe Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57; M15L, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT Giu Giu Giy Vai Ser Leu Asp Lys Arg Giu Vai Vai Arg Giu Vai Cys Ser Giu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Leu lle Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIY Lys Cys Ala Pro Phe Phe Tyr Giy Giy Cys Giy Giy Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 14

pBG028

α-factor

ATG AGA TIT CCT TCA ATT TIT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57; M15L, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA TTG ATC TAC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT AAC TAG ATG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Leu IIe Tyr Arg Trp Tyr Phe Asp Vai Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHl

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala ile



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 15

pTW6183

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

KPI(-4-57; I16H, S17F)

Xbal

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Giu Val Val Arg Giu Val Cys Ser Giu Gin

Rsrll

Agel Aatil

GCT GAG ACC GGT CCG TGC CGT GCA ATG <u>CAC</u> <u>TTC</u> CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC <u>GTG AAG</u> GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Alá Met His Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pTW6184

FIG. 16

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lie Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG IIIe Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lie Asn Thr Thr lie Ala Ser lie Ala Ala Lys

Xbal

KPI(-4-57; I16H, S17Y)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gln

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA ATG <u>CAC</u> <u>TAC</u> CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC <u>GTG ATG</u> GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Met His Tyr Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lie



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

pTW6185

FIG. 17

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

Ala Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln Ile Pro Ala Glu Ala Val

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA
TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT

Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser ile Ala Ala Lys

Xbal

KPI(-4-57; I16H, S17W)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

RsrII

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA ATG <u>CAC</u> <u>TGG</u> CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT TAC <u>GTG</u> <u>ACC</u> GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Met His Trp Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pTW6173

FIG. 18

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG ALA Pro Val Asn Thr Thr Thr Glu Asp Glu Thr Ala Gln lle Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe IIe Asn Thr Thr IIe Ala Ser IIe Ala Ala Lys

Xbal

KPI(-4-57; M15A, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

Rsrli

Agel

AatII

GCT GAG ACC GGT CCG TGC CGT GCA GCT CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG

Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pTW6174

FIG. 19

α-factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser IIe Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC
TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG

Ile Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lle Asn Thr Thr lle Ala Ser lle Ala Ala Lys

Xbal

KPI(-4-57; M15L, I16H)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT GIU GIU GIU GIU Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

RsrII

Agel

AatII

GCT GAG ACC GGT CCG TGC CGT GCA TTG CAC TCC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT AAC GTG AGG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Leu His Ser Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Phe Asp

BamHI

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Ala lle



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 20

KPI(-4-57; M15A, S17W) TW6165

Glu - Thr - Gly - Pro - Cys - Arg - Ala -
$$\underline{Ala}$$
 - Ile - \underline{Trp} - Arg 8 9 10 11 12 13 14 15 16 17 18



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 21

KPI(-4-57; M15A, S17Y) TW6166

Glu - Thr - Gly - Pro - Cys - Arg - Ala -
$$\underline{Ala}$$
 - Ile - \underline{Tyr} - Arg 8 9 10 11 12 13 14 15 16 17 18



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 22

KPI(-4-57; M15L, S17F) TW6175



Title: PROTEASE INHIBITOR

PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 23

KPI(-4-57; M15L, S17Y) BG028



Title: PROTEASE INHIBITOR

PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 24

KPI(-4-57; I16H, S17F) TW6183



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 25

KPI(-4-57; I16H, S17Y) TW6184



Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 26

KPI(-4-57; I16H, S17W) TW6185

Glu - Thr - Gly - Pro - Cys - Arg - Ala - Met -
$$\frac{\text{His}}{10}$$
 - $\frac{\text{Trp}}{10}$ - Arg 8 9 10 11 12 13 14 15 16 17 18



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 27

KPI(-4-57; M15A, S17F) DD185



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 28

KPI(-4-57; M15A, I16H) TW6173

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Title: PROTEASE INHIBITOR

PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 29

KPI(-4-57; M15L, I16H) TW6174

Glu - Thr - Gly - Pro - Cys - Arg - Ala -
$$\underline{\text{Leu}}$$
 - $\underline{\text{His}}$ - Ser - Arg 8 9 10 11 12 13 14 15 16 17 18



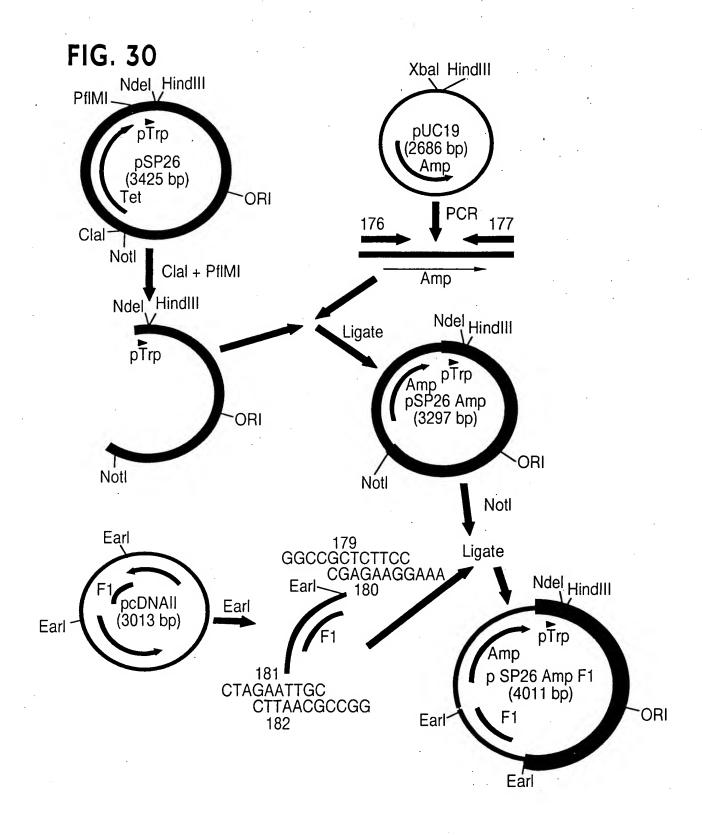




FIG. 31

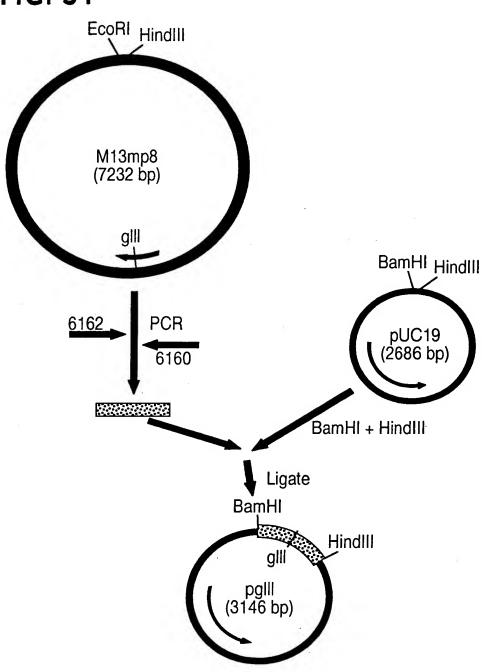




FIG. 32

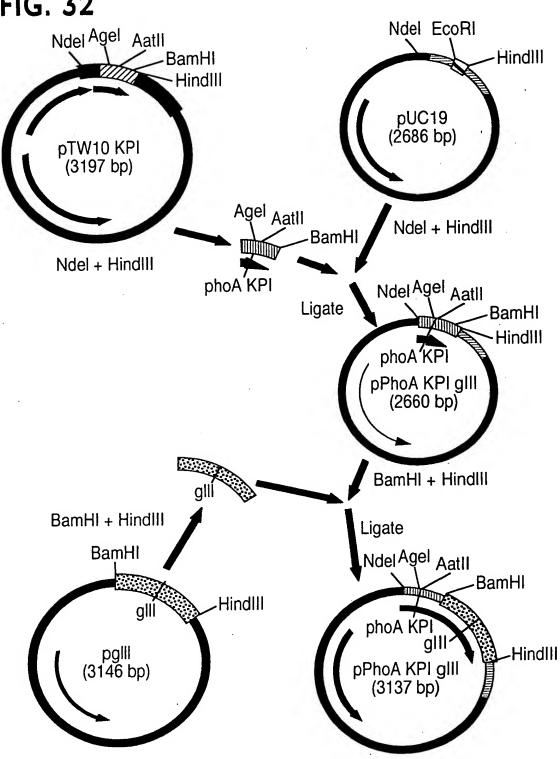
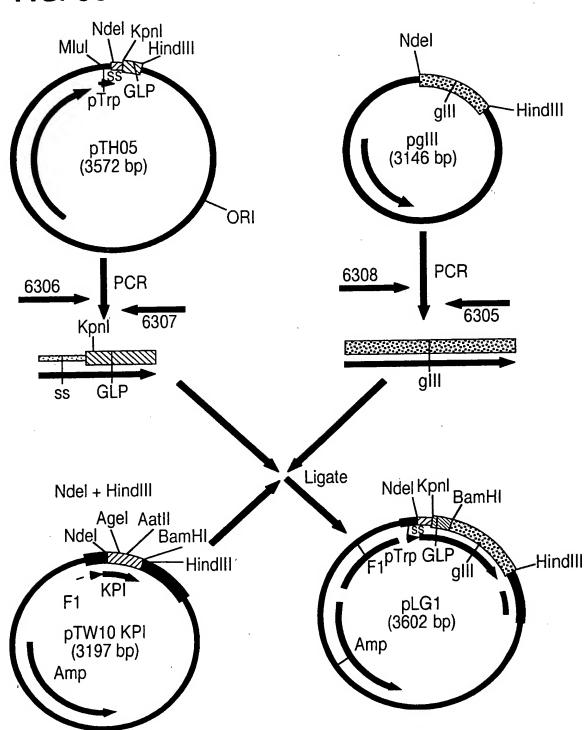




FIG. 33





Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

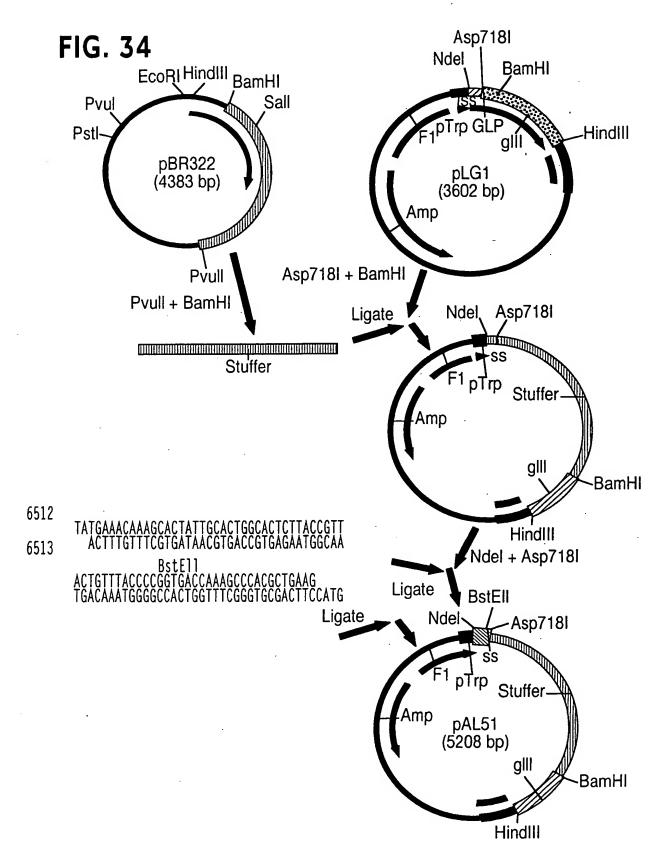




FIG. 35

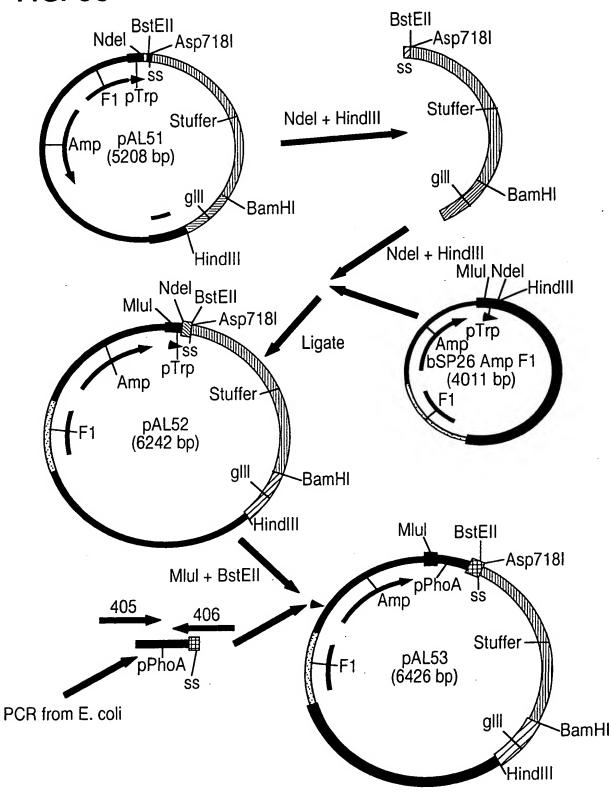
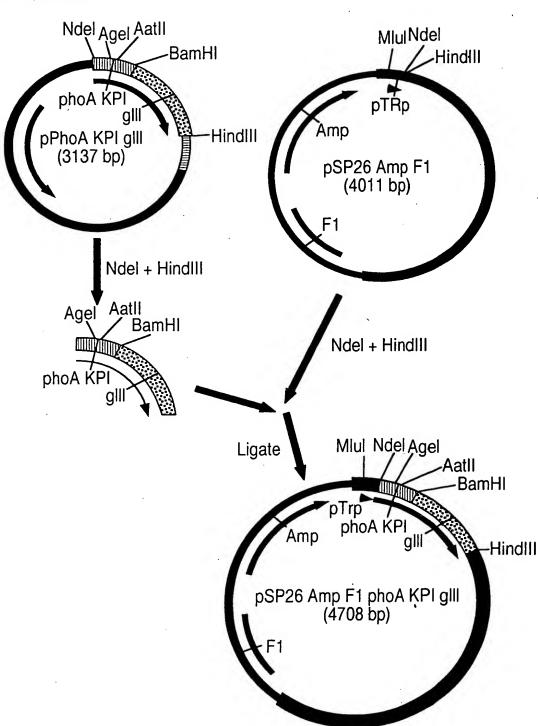


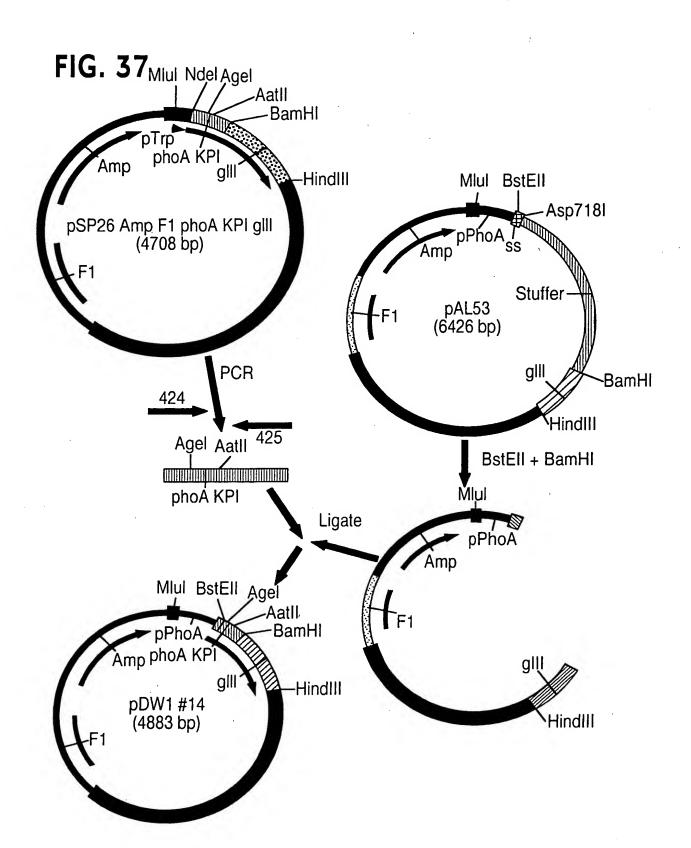


FIG. 36





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604



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Title: PROTEASE INHIBITOR PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

phoA signal

FIG. 38

BstEll

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA Val Lys Gin Ser Thr lie Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55) ___ Agel

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA ATG ATC TCC CGC TGG

Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Met ile Ser Arg Trp

Aatll

TAC TIT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC

Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

BamHI

C ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA

• GIy Ser GIy Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys GIy Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT ASp Tyr Gly Ala Ala lie Asp Gly Phe lie Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT IN GIV Ala Thr GIV Asp Phe Ala GIV Ser Asn Ser GIN Met Ala GIN Val GIV Asp GIV Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA

ASn Ser Pro Leu Met Asn Asn Phe Arg Gin Tyr Leu Pro Ser Leu Pro Gin Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA VCs Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser Ile Asp Cys Asp Lys

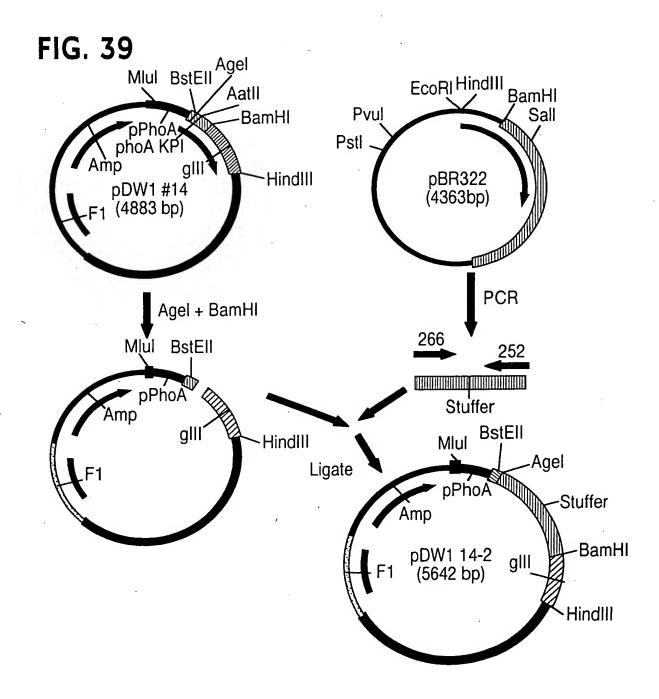
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TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA

Phe Ser Thr Phe Ala Asn IIe Leu Arg Asn Lys Glu Ser •••



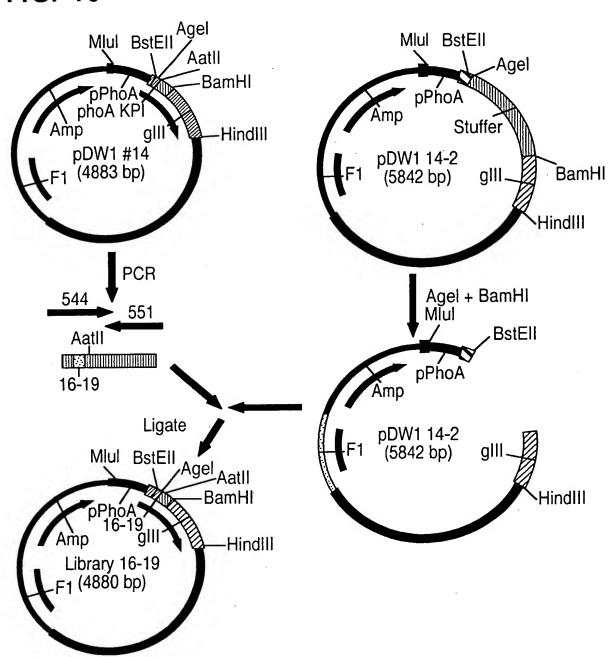
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 40



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Title: PROTEASE INHIBITOR PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

phoA signal

FIG. 41

BstEII

GTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA

Val Lys Gln Ser Thr lie Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

KPI (1-55; 16 - 19)

Agel

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT NNS NNS NNS NNS TGG TAC

Ala Glu Val Cys Ser Glu Gin Ala Glu Thr Gly Pro Cys Arg --- --- Trp Tyr

Aatll

TTT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT

Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg

AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGC TCT GGT

Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Val Cys Gly Ser Gly Gly Gly Ser Gly

TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA AAT Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu Asn

GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT GAT Ala Asp Glu Asn Ala Leu Gin Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr Asp

TAC GGT GCT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT GGT

Tyr Gly Ala Ala lie Asp Gly Phe lie Gly Asp Val Ser Gly Leu Ala Asn Gly Asn Gly

alli

GCT ACT GGT GAT TTT GCT GGC TCT AAT TĆC CAA ATG GCT CAA GTC GGT GAC GGT GAT AAT
Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp Asn

TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA TGT

Ser Pro Leu Met Asn Asn Phe Arg Gin Tyr Leu Pro Ser Leu Pro Gin Ser Val Glu Cys

CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA ATA
Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser IIe Asp Cys Asp Lys IIe

AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA TTT AS AS Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val Phe

TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA

Ser Thr Phe Ala Asn lie Leu Arg Asn Lys Glu Ser • • •

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Title: PROTEASE INHIBITOR PEPTIDES

Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

phoA signal

FIG. 42

BstEll

OTG AAA CAA AGC ACT ATT GCA CTG GCA CTC TTA CCG TTA CTG TTT ACC CCG GTG ACC AAA

Val Lys Gln Ser Thr lie Ala Leu Ala Leu Leu Pro Leu Leu Phe Thr Pro Val Thr Lys

LDL (1 55, M15A, C175)

KPI (1-55; M15A, S17F)

GCC GAG GTG TGC TCT GAA CAA GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG
Ala Glu Val Cys Ser Glu Gln Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Phe Arg Trp

Aatll

TAC TIT GAC GTC ACT GAA GGT AAG TGC GCT CCA TTC TIT TAC GGC GGT TGC GGC GGC AAC

Tyr Phe Asp Val Thr Glu Gly Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn

CGT AAC AAC TTT GAC ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GGT GGT GGC TCT

Arg Asn Asn Phe Asp Thr Glu Glu Tyr Cys Met Ala Vai Cys Gly Ser Gly Gly Gly Ser

GGT TCC GGT GAT TTT GAT TAT GAA AAG ATG GCA AAC GCT AAT AAG GGG GCT ATG ACC GAA

Gly Ser Gly Asp Phe Asp Tyr Glu Lys Met Ala Asn Ala Asn Lys Gly Ala Met Thr Glu

AAT GCC GAT GAA AAC GCG CTA CAG TCT GAC GCT AAA GGC AAA CTT GAT TCT GTC GCT ACT Asn Ala Asp Glu Asn Ala Leu Gln Ser Asp Ala Lys Gly Lys Leu Asp Ser Val Ala Thr

GAT TAC GGT GCT ATC GAT GGT TTC ATT GGT GAC GTT TCC GGC CTT GCT AAT GGT AAT
ASp Tyr Gly Ala Ala lle Asp Gly Phe lle Gly Asp Val Ser Gly Leu Ala Asn Gly Asn

GGT GCT ACT GGT GAT TTT GCT GGC TCT AAT TCC CAA ATG GCT CAA GTC GGT GAC GGT GAT Gly Ala Thr Gly Asp Phe Ala Gly Ser Asn Ser Gln Met Ala Gln Val Gly Asp Gly Asp

AAT TCA CCT TTA ATG AAT AAT TTC CGT CAA TAT TTA CCT TCC CTC CCT CAA TCG GTT GAA
ASn Ser Pro Leu Met Asn Asn Phe Arg Gln Tyr Leu Pro Ser Leu Pro Gln Ser Val Glu

TGT CGC CCT TTT GTC TTT GGC GCT GGT AAA CCA TAC GAA TTT TCT ATT GAT TGT GAC AAA

Cys Arg Pro Phe Val Phe Gly Ala Gly Lys Pro Tyr Glu Phe Ser IIe Asp Cys Asp Lys

ATA AAC TTA TTC CGT GGT GTC TTT GCG TTT CTT TTA TAT GTT GCC ACC TTT ATG TAT GTA File Asn Leu Phe Arg Gly Val Phe Ala Phe Leu Leu Tyr Val Ala Thr Phe Met Tyr Val

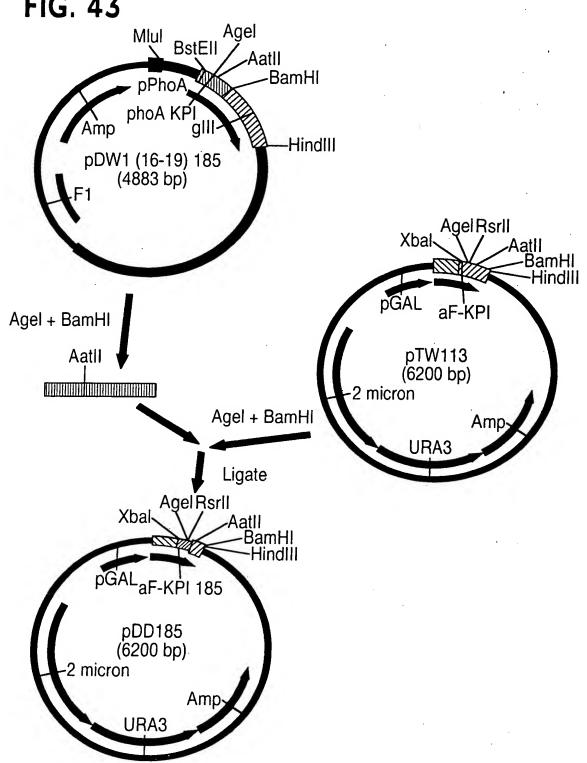
TTT TCT ACG TTT GCT AAC ATA CTG CGT AAT AAG GAG TCT TAA TA

Phe Ser Thr Phe Ala Asn lie Leu Arg Asn Lys Glu Ser



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 43





Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

pDD185

FIG. 44

α -factor

ATG AGA TTT CCT TCA ATT TTT ACT GCA GTT TTA TTC GCA GCA TCC TCC GCA TTA GCT TAC TCT AAA GGA AGT TAA AAA TGA CGT CAA AAT AAG CGT CGT AGG AGG CGT AAT CGA

Met Arg Phe Pro Ser lie Phe Thr Ala Val Leu Phe Ala Ala Ser Ser Ala Leu Ala

GCT CCA GTC AAC ACT ACA ACA GAA GAT GAA ACG GCA CAA ATT CCG GCT GAA GCT GTC CGA GGT CAG TTG TGA TGT TGT CTT CTA CTT TGC CGT GTT TAA GGC CGA CTT CGA CAG Ala Pro Val Asn Thr Thr Glu Asp Glu Thr Ala Gin IIe Pro Ala Glu Ala Val

ATC GGT TAC TTA GAT TTA GAA GGG GAT TTC GAT GTT GCT GTT TTG CCA TTT TCC AAC TAG CCA ATG AAT CTA AAT CTT CCC CTA AAG CTA CAA CGA CAA AAC GGT AAA AGG TTG IIe Gly Tyr Leu Asp Leu Glu Gly Asp Phe Asp Val Ala Val Leu Pro Phe Ser Asn

AGC ACA AAT AAC GGG TTA TTG TTT ATA AAT ACT ACT ATT GCC AGC ATT GCT GCT AAA TCG TGT TTA TTG CCC AAT AAC AAA TAT TTA TGA TGA TAA CGG TCG TAA CGA CGA TTT Ser Thr Asn Asn Gly Leu Leu Phe lie Asn Thr Thr lie Ala Ser lie Ala Ala Lys

Xbal

KPI(-4-57; M15A, S17F)

GAA GAA GGG GTA TCT CTA GAT AAA AGA GAG GTT GTT AGA GAG GTG TGC TCT GAA CAA CTT CTT CCC CAT AGA GAT CTA TTT TCT CTC CAA CAA TCT CTC CAC ACG AGA CTT GTT I Glu Glu Gly Val Ser Leu Asp Lys Arg Glu Val Val Arg Glu Val Cys Ser Glu Gin

Rsrll

Agel

Aatll

GCT GAG ACC GGT CCG TGC CGT GCA GCT ATC TTC CGC TGG TAC TTT GAC GTC ACT GAA CGA CTC TGG CCA GGC ACG GCA CGT CGA TAG AAG GCG ACC ATG AAA CTG CAG TGA CTT Ala Glu Thr Gly Pro Cys Arg Ala Ala lle Phe Arg Trp Tyr Phe Asp Val Thr Glu

GGT AAG TGC GCT CCA TTC TTT TAC GGC GGT TGC GGC GGC AAC CGT AAC AAC TTT GAC CCA TTC ACG CGA GGT AAG AAA ATG CCG CCA ACG CCG CCG TTG GCA TTG TTG AAA CTG GIy Lys Cys Ala Pro Phe Phe Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Asp

BamHi

HindIII

ACT GAA GAG TAC TGC ATG GCA GTG TGC GGA TCC GCT ATT TAA GCT T
TGA CTT CTC ATG ACG TAC CGT CAC ACG CCT AGG CGA TAA ATT CGA A

Thr Giu Giu Tyr Cys Met Ala Vai Cys Gly Ser Ala lie



Title: PROTEASE INHIBITOR PEPTIDES

Inventor(s): R. Tyler WHITE et al.

Appl. No.: 10/076,604

FIG. 45

Plasma kallikrein inhibition by KPI (-4-57) variants

Variant		•	Substitution		K.(nM)
ì		15	16	17	
	KPI (4-57)				45.00
	KPI (4-57; M15A, S17F)	∢	·	吐	0.39
	KPI (4-57; M15A, S17W)	4		M	0.65
	KPI (4-57; M15A, S17Y)	4		>	0.40
	KPI (4-57; M15L, S17F)	ᆸ		Ľ	0.50
	KPI (4-57; M15L, S17Y)	J		⊁	1.10
	KPI (4-57; 116H, S17F)		Ħ	吐	1.20
	KPI (-4-57; 116H, S17Y)		Н	> -	0.91
TW6185	KPI (-4-57; 116H, S17W)		Ħ	×	1.30
	KPI (4-57; M15A, 116H)	⋖	н		1.00
	KPI (4-57; M15L, 116H)	Ļ	Ħ		06.0



Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 46A

			Inhibition Ki (nM)	Ki (nM)	
Variant	Sequence	kallikrei	Plasmin	Z IZ	Z.
Aprotinin '	RPDFCLEPPYTGPCKARI I RYFYNAKAGLOQTFVYGGCRAKRNNFKSARDCHRTCGGA	20.00	0.23	5000.0	
Aprotinin R15, S42	DFCLEPPYTGPCRARI IRYFYNARAGLOQTFVYGGCRAKSNNFKSAEDCHRTCGGA	16:0	0.17	3983.0	
KPI (4-57)	EVVREVCSEQAETGPCRAMISRHYPDVTEGRCAPFFYGGCGGNRNNFDTERYCHAVCGSAI	45.00	34.00	3718.0	161.0
TW6167	EVVREVCSEQAEPGPCRAMISRHYFDVTEGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	91.00		3641.0	288.0
BG031	EVVRBVCSEQAEVGPCRAMISRMYFDVTEGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	34.00		498.0	
BG032	EVVREVCSEQAESGPCRAMISRHYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	49.00		731.0	
TW101	EVCSEQAETGPCKAHISRHYFDVTEGKCAPPPYGGCGGNRNNPDTEEYCHAVCGSAI	2000.00	11.50		
TW6208	EVVREVCSEQAETGPCRGHISRWYPDVTEGKCAPPFYGGCGGNRNNFDTEBYCHAVCGSAI			369.0	
TW106	EVCSEQAETGPCRARISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	260.00	3.70		
DD108	EVVREVCSEQAETGPCRAAISRMYPDVTEGKCAPPYGGCGGNRNNFDTEEYCMAVCGSAI	1.30	11.20	1600.0	123.0
DD109	BUVREVCSEQAETGPCRAIISRHYFDUTEGKCAPFFYGGCGGNRNNFDTEBYCHAVCGSAI	9.50		0.1891	421.0
00110	EVVREVCSEQAETGPCRAL I SRHYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	2.10		624.0	55.0
11100	EVVREVCSEQAETGPCRASISRMYFDVTBGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	99'5			
DD112	BVVRBVCSEQAETGPCRAVISRWYFDVTEGKCAPPPYGGCGGNRNNFDTEBYCMAVCGSAI	08.9		998.0	
TW6179	EVVREVCSEQAETGPCRAGISRMYFDVTEGKCAPPTYGGCGGNRNNFDTEBYCKAVCGSAI	78.00		368.0	



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TW/173		ŀ			
601041	BVVKEVCSEQAETGPCRAMHSRMYFDVTEGRCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	6.3	103.58	4532.0	457.0
TW6172	EVVRBVCSEQAETGPCRAMASRHYFDVTEGRCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	315.00			1463.0
TW6180	EVVREVCSEQAETGPCRAMFSRWYFDVTBGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	90.02		885.0	39.0
TW6181	BVVREVCSEQAETGPCRAHKSRWYFDVTBGKCAPFFYGGCGGNRNNFDTEBYCHAVCGSAI	150.00		15140	
BG001	BVVREVCSEQAETGPCRAMLSRWYFDVTBGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	38.00	9.0	489.0	204.0
TW116	BVCSEQAETGPCRAMIIRHYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	145.00	89.00		806.0
DD102	EVVREVCSEQAETGPCRAMIPRHYFDVTBGKCAPFYGGCGGNRNNFDTERYCMAVCGSAI	16.00		315.0	
DD103	EVVREVCSEQAETGPCRAHIPRHYPDVTEGKCAPPPYGGCGGNRNNFDTEEYCMAVCGSAI	17.00		2128.0	110.0
DD104	EVVREVCSEQAETGPCRAMIYRMYFDVTEGKCAPFPYGGCGGNRNNFDTEBYCMAVCGSAI	15.00		237.0	3450
DD105	EVVREVCSEQAETGPCRAHIWRWYFDVTEGKCAPFFYGGCGGNRNNFDTEBYCMAVCGSAI	18.00		1980	320.0
TW6168	EVVREVCSEQAETGPCRAHILRHYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	25.80		3521.0	395.0
TW6182	BVVREVCSEQAETGPCRAMIHRWYPDVTEGKCAPFPYGGCGGNRNNFDTEBYCMAVCGSAI	36.00		752.0	
TW6194	EVVREVCSEQAETGPCRAMIERWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	70.83	T		
TW6210	BVVREVCSEQAETGPCRAHIQRHYPDVTEGKCAPPPYGGCGGNRNNPDTEEYCHAVCGSAI	24.00		9770	
907J	EVVREVCSEQAETGPCRAMISAMYPDVTEGKCAPFFYGGCGGNRNNFDTEEYCKAVCGSAI	110 20		000%	133.0
BG012	EVVREVCSEQAETGPCRAMISTWYFDVTEGRCAPFPYGGCGGNRNNFDTEEYCMAVCGSAI			900	1160



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TW6209	EVVREVCSEQAETGPCRAMISHWYPDVTBGKCAPPYGGGGGURNNPDTERYCMAVCSSAT	8100	06 57	1840	613.0
TW6211	EVVREVCSEQAETGPCRAMISKHYPDVTRGKCAPPPYGGCGGNRNNPDTERYCMAVCGSAT	184 00	2	0.00	0.010
DD128	EVVREVCSEQAETGPCRAHISLHYPDVTEGKCAPFFYGGCGGNRNNFDTEBYCMAVCSSAI	44.00		77	37.0
TW6142	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPFVYGGCGGNRNNPDTEBYCMAVCGSAI	18.00	18.00	7972.0	2250
AL301	EVVREVCSEGAETGPCRAMISRHYPDVTEGKCAPPLYGGCGGNRNNFDTEBYCMAVCGSAI	216.00		15570	
AL302	EVVREVCSEQAETGPCRAHISRHYPDVTBGKCAPFGYGGCGGNRNNFDTBBYCHAVCGSAI	39.00			316.0
TW6147	EVVREVCSEQAETGPCRAHISRHY PDVTEGKCAPP PYGGCAGNRNN PDTEBYCHAVCGSAI	35.00		0.0601	179.0
TW6138	EVVREVCSEQAETGPCRAMISRHYFDVTEGKCAPFFYGGCKGNRNNFDTEEYCHAVCGSAI	8. 8. 8.		921.0	309.0
TW6154	EVVREVCSEQAETGPCRAHISRHYPDVTEGKCAPFFYGGCLGNRNNFDTEBYCMAVCGSAI	11.00		9150	39.0
TW6155	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPFFYGGCHGNRNNFDTEEYCHAVCGSAI	11.00			270
TW6140	EVVREVCSEQAETGPCRAHISRHYPDVTEGKCAPPPYGGCNGNRNNPDTEBYCHAVCGSAI	35.00		4750	
TW6156	EVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCPGNRNNFDTEEYCMAVCGSAI				
TW6141	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPFFYGGCQGNRNNPDTEBYCMAVCGSAI	42.00			
TW118	EVCSEQAETGPCRAHISRWYFDVTBGKCAPFFYGGCRGNRNNFDTBBYCHAVCGSAI	909	24 00	130000	680
DD100	EVVREVCSEQAETGPCRAHISRWYFDVTEGKCAPFFYGGCCGNRNNFDTEBYCMAVCGSAI	1500			3
TW6157	EVVREVCSEQAETGPCRAHISRWYFDVTEGRCAPFFYGGCSGNRNNFDTEBYCMAVCGSAI	90.07		8110	168.0
TW6158	EVVREVCSEQAETGPCRAHISRHYFDVTEGKCAPFFYGGCTGNRNNFDTEEYCHAVCGSAI	29.00			



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FIG. 46D

THIS 160	•		Ì	I	
1 40139	EVVREVCSBOAETGPCRAMISRMYPDVTBGKCAPPPYGGCVGNRNNPDTEBYCMAVCGSAI	17.00			64.0
TW6161	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPPYGGCYGNRNNPDTERYCMAVCGSAI	25	28.08	1507.0	2
DDI01		ST TY	3	0.100	3
TW6151	EVVREVCSEQAETGPCRAMISRMYPDVTEGKCAPPRYGGCEGNRNNFDTERYCMAVCGSAI	161.00		11630	0540
TW6139	EVVREVCSEQAETGPCRAMISRHYPDVTEGKCAPPYGGCHGNRNNFDTERYCHAVCGSAI	19 00	22 RA	130	78.0
TW6153	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPPFYGGCIGNRNNPDTERYCMAVCGSAI	8	30	650	360
TW122	EVCSEQAETGPCRAMISRHYPDVTEGKCAPPYGGCGANRNNPDTERYCHAVCGSAI	32.00	27.00		5810
TW6178	BVVREVCSEQAETGPCRAHISRHYPDVTEGKCAPPPYGGCGRNRNNPDTBBYCMAVCGSAI	16.00		440	
TW6148	EVVREVCSEQAETGPCRAMISRWY PDVTEGKCAPPFYGGCGGARNN PDTEBYCHAVCGSAI	900			
TW124	EVCSEQAETGPCRAMISRWYPDVTBGKCAPPPYGGCGGNSNNPDTEEYCMAVCGSAI	62.50	08.8		
TW6149	EVVREVCSEQAETGPCRAMISRWYPDVTEGKCAPPPYGGCGGNANNPDTEEYCMAVCGSAI	24.00			
TW6173	EVVREVCSEQAETGPCRAAHSRWYPDVTEGKCAPPYGGCGGNRNNPDTERYCMAVCYSAT	8	174	1432 0	
TW6174	EVVREVCSEQAETGPCRALHSRWYPDVTEGKCAPPYGGCGGNRNNPDTERYCMAVCGSAT	8 8	989	270%	
BG002	EVVREVCSEQAETGPCRALLSRWYPDVTEGKCAPFFYGGOGGNRNNPDTERYCMAVGSSAT	860	200	0.07.14 A01.0	007
DD129	EVVREVCSEQAETGPCRALFSRWYFDVTEGKCAPFYGGCGGNRNNFDTEEYCMAVCGSAT	36.	3	1864.0	9 6
DD185	EVVREVCSEQAETGPCRAA I PRWY PDVTEGRCA P P PYGGCGGNRNN PDTEEY CMAVCGSA I	630	871	1200	180



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FIG. 46E

TW6165	EVVREVCSEQAETGPCRAAIHRHYFDVTEGKCAPFFYGGCGGNRHNFDTEEYCMAVCGSAI	99'0	16.40	206.0	
TW6166	EVVREVCSEQAETGPCRAAIYRWY PDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	0.4	10.10	73.0	
BG028	EVVREVCSEQAETGPCRALIYRHYPDVTEGKCAPFFYGGCGGNRNNFDTBEYCHAVCGSAI	1.10	12.10	93.8	
TW6169	EVVREVCSEQAETGPCRALILRHYPDVTEGKCAPFFYGGCGGNRNNFDTBEYCHAVCGSAI	1.20		619.0	111.0
DD113	EVVREVCSEQAETGPCRALIPRWYPDVTEGKCAPFYGGCGGNRNNFDTBEYCMAVCGSAI	0.85	12.80	293.0	74.0
TW6175	Evvrevcsegaetgpcralifrwyfdvtegkcapppyggcggnrnpdteeychavcgsai	0.50	7.46	35.0	9.95
TW6201	EVVRBVCSEQAETGPCRAGIYRHY PDVTEGKCAPF PYGGCGGNRNN PDTEEY CHAVCGSAI	34.60		419.0	
TW6202	EVVREVCSEQAETGPCRAGIHRHY PDVTEGKCAPF PYGGCGGNRNN PDTEBYCHAVCGSAI	128.50		1237.0	
TW6203	EVVREVCSEQAETGPCRAGIPRHY PDVTEGKCAPF PYGGCGGNRNN PDTBEYCHAVCGSAI	31.20		5045.0	
TW6204	EVVREVCSEQAETGPCRAA I SAHY PDVTEGKCAPF PYGGCGGNRNN PDTEEY CHAVCGSA I		,	147.0	87.0
TW6205	EVVRBVCSEQAETGPCRALISAHY FDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI			195.0	29.0
DD114	EVVREVCSEQAETGPCRAA I SRHY FDVTEGKCAPP PYGGCRGNRNN FDTEEYCHAVCGSA I	0.70	1.11	224.0	
TW6190	EVVREVCSEQAETGPCRAAISRHYFDVTEGKCAPFFYGGCYGNRNNFDTEEYCHAVCGSAI	0.83	52.20	589.0	13%.0
TW6183	EVVREVCSEQAETGPCRAMHFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	1.20	11.68	12440.0	159.0
TW6184	EVVREVCSEQAETGPCRAHHYRWYPDVTEGKCAPPPYGGCGGNRNNPDTBEYCMAVCGSAI	16'0	11.96	14000.0	214.0
TW6185	EVVREVCSEQALTGPCRAMHWRWY PDVTEGKCAPP PYGGCGGNRNN PDTEEY CHAVCGSAI	1.30	18.60	388.0	473.0
BG003	EVVREVCSEQAETGPCRAMLHRHYPDVTEGKCAPPFYGGCGGNRNNFDTEEYCHAVCGSAI	36.00		467.0	



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FIG. 46F

TW6186	EVVREVCSEQAETGPCRAMHSRWYPDVTEGKCAPFFYGGCYGNRNNFDTBEYCMAVCGSAI	0.48	8.86	186.0	11.0
TW6187	EVVREVCSEQAETGPCRAMIFRWYPDVTEGRCAPFFYGGCYGNRNNFDTEEYCMAVCGSAI	3.80	15.40	92.0	15.0
TW6188	EVVRBVCSEQAETGPCRAMIYRWYPDVTEGKCAPPFYGGCYGNRNNFDTBEYCMAVCGSAI	6.4		419.0	24.0
TW6189	EVVREVCSEGAETGPCRAMIWRWYFDVTEGKCAPFFYGGCYGNRNNFDTBEYCMAVCGSAI	4 .00			34.0
TW6170	EVVREVCSEQAEPGPCRAL I LRWY FDVTEGKCAPPY GGCGGNRNN FDTEBY CHAVCGSAI	2.50			452.0
00115	EVVREVCSEQAETGPCRGY I TRWY PDVTEGKCAP F F Y GGCGGNRNN PDTEEY CMAVCGSAI			213.0	299.0
DD170	EVVREVCSEQAETGPCRALHNRWY PDVTEGKCAPFFYGGCGGNRNNFDTBEYCMAVCGSAI	0.99	18.00	550.0	
TW6176	EVVREVCSEQAETGPCRAAHPRWYFDVTEGKCAPPFYGGCGGNRNNFDTEEYCMAVCGSAI	3,50	118.00	9.95	
TW6177	EVVREVCSEQAETGPCRALHFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	7.20	32.70	245.0	156.0
BG006	EVVREVCSEQAETGPCRAALFRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	0.30	12.10	80.0	
DD130	EVVREVCSEGAETGPCRALFTRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCHAVCGSAI	5.50	-		9.5
DD131	EVVREVCSEQAETGPCRAL PKRWY FDVTEGKCAP FYGGCGGNRNN FDTBEYCHAVCGSAI	7.90	2.00	1385.0	3.3
DD132	EVVREVCSEGAETGPCRAPPKRWYFDVTEGKCAPPYGGCGGURNNFDTEEYCHAVCGSAI	112.00			16.8
DD120	BVVREVCSEGAETGPCRAAFSAWYFDVTEGKCAPFFYGGCGGNRNNFDTBEYCMAVCGSAI	8.30			0
DD121	EVVREVCSEQAETGPCRALLSAWYFDVTEGKCAPPFYGGCGGNRNNFDTBEYCMAVCGSAI	19.00			21.0
BG014	EVVREVCSEQAETGPCRALIHHMY POVTEGRCAPPY GGCGGNRNN POTEBY CHAVCGSAI	9.20	18.70	18.0	



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מוסס	EVVREVCSEQAETGPCRALI FAHY FDVTEGKCAPFYGGOGGNRNNFDTEEYCMAVCGSAT	15.00			46.0
BG015	EVVREVCSEQAETGPCRALIYHYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	909	12.20	19.4	597.0
BG020	EVVREVCSEQAETGPCRAAIHKWYPDVTEGKCAPFFYGGOGGRRNNFDTEEYCMAVOGSAI	1.70		10,901	
BG022	BVVREVCSEQAETGPCRAAIYHWYPDVTEGKCAPFFYGGCGGNRNNPDTEEHCMAVCGSAI	19.0	7.26	<u>₹</u>	
BG023	EVVREVCSEGAETGPCRALI QHWY PDVTEGKCAPP FYGGOGGNRNN PDTEEY CMAVOGSAI	23.00		262.0	
BG024	EVVREVCSEQAETGPCRALIYKWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAI	01.4	7.47	38.7	
BG027	BVVRBVCSEQAETGPCRAAI QHHY PDVTEGKCAPP PYGGCGGNRNN PDTBEY CHAVCGSAI	5.80		14.0	
DD116	EVVREVCSEQARIGPCRAAI FRWY FDVTEGKCAP PYGGCRGNRNN FDTERYCMAVCGSAI	0.14		583.0	20.20
TW6191	Evvrevcse califpani prwy poutegrcappy ggcygnrny dtery cmancgsai	0.26		0.499	200
DD117	EVVREVCSEQAETGPCRAL I PRWY FDVTEGRCAPPY GGCRGNRNN FDTEBY CMAVCGSA I	0.11	·	1034.0	99.0
BG029	EVVREVCSEQAEVGPCRALIYHWYFDVTEGKCAPFYGGCGGNRNNFDTEEYCMAVCGSAI	3.20		7.9	
BG030	EVVREVCSEGARSGPCRALIYHHYPDVTEGKCAPPYGGGGGNRNNPDTEEYCMAVCGSAI	09.7		26.1	
BG033	Evvrevcseqaevgpcraaiyhhyfdvtegkcapppygggggnrnpdteehcmavcgsai	0.75		5.6	



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FIG. 46F

BG034	EVVREVCSEQAESGPCRAAIYHWYFDVTEGKCAPFYGGCGGNRNNFDTEEYCMAVCGSAI	0.47		18.5	
BG040	EVVREVCSEQAEIGPCRALIYHMYFDVTEGKCAPRFYGGOGGNRNNFDTEEYCMAVCGSAI	340		98	
BG016	EVVREVCSEQAETGPCRGAIQHWYPDVTEGKCAPPTYGGCGGNRNNFDTEEYCMAVCGSAI	160.00		178.0	
BG017	EVVREVCSEQAETGPCRGAIRHMY PDVTEGKCAP PYGGGGGNRNN FDTEEY CMAVCGSAI	180.00		2000	
BG021	EVVREVCSRQAETGPCRGSIRHWYPDVTEGKCAPFYGGCGGURNNFDTEBYCMAVCGSAI	340,00		224.0	
BG025	EVVREVCSEQAETGPCRGLIYHWY PDVTEGRCAPPFYGGCGGNRNN PDTEEYCMAVCGSAI	00.59		162	
BG026	EVVREVCSEQAETGPCRGAI YHWYPDVTEGKCAPPYGGOGGNRNNFDTEEYCMAVCGSAI	20.00		34.9	
DD118	EVVREVCSEQAETGPCRALHNRWYPDVTEGKCAPPYGGCRGNRNNFDTEEYCHAVCGSA 1	0.53			
DD134	EVVRBVCSEQAETGPCRALPKRMYPDVTEGKCAPPYGGCYGNRNNFDTEEYCMAVCGSAI	91	2	15640 0	90
DD135	EVVRBVCSEQAETGPCRALFKRMYPDVTEGKCAPFFYGGCLGNRNNFDTEEYCMAVCGSAI	130		74730	60
DD136	EVVREVCSEQAETGPCRALFKRWYPDVTEGKCAPFPYGGCHGNRNNFDTEEYCMAVCGSAI	9.1			1.8



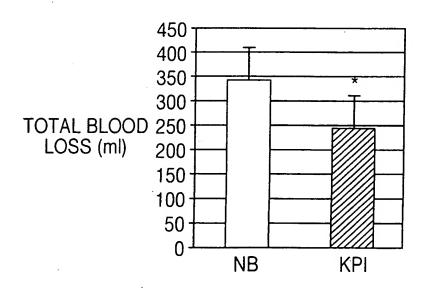
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 47

VOLUMES

NS		344.25	
KPI		245.75	
-	KPI	NS	
		298	366
		266	342
		354	294
		258	385
		168	288
		266	469
		172	338
		184	272

MEAN 245.75 344.25 66.2414415 63.97488346 STDEV TTEST 0.009094999





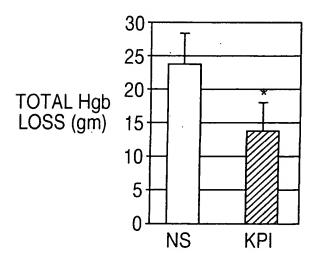
Inventor(s): R. Tyler WHITE et al. Appl. No.: 10/076,604

FIG. 48

HEMOGLOBIN

NS	23.61
KPI	13.59

			4		
	KPI		NS		
		16.58		24.	95
		15.19		24.	87
		20.21		20.	46
		8.99		27.	59
		14.63		18.	23
		15.31		31.	59
		7.7		23.	26
		10.14		17.	96
MEAN	13.	59375	23.	613	75
STDEV	4.2	61438	4.	687	61
TTEST			0.0	005	36





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FIG. 49

Basel	Baseline PaO2	a02	End CPB		Obs 60 min	.u	Obs 180 min	0 min	
KPI	4	NS	KPI	NS	KPI	NS	KPI	NS	
652.2	7	6.029	495.7	60.5	483.7	441.3		က	391.3
. •	654	559.2	444.6	132.2	330.1	448.7	264.1		484.6
29	596.2	622.9	170.2	93.8	415.4	85.1	416.5		81.3
09	606.2	689.2	264.2	333.9	430.2	529.6	361.9		333.2
63	633.1	665.1	567.2	341.7	613	568.3	8.06		546.6
	646.6	527	507.4	226.9	564.3	438.1	518.2		485.3
56	563.2	461.7	547.1	89.1	501	42.6	494.2		45.6
	626.9	508	416.6	59.7	504.5	405.8	— 4	452	383.7
626.	626.425	588	426.625	426.625 167.225	480.275 369.938	369.938	371.1		344
TDEV 34.46	92 8	34.4692 85.5055	140.474	140.474 117.993	88.6187 196.523	196.523	150.277	7 18	186.22
	က	9			6	Ŋ		4	
	=d	0.268	=d,	0.0014	_d	p = 0.17915		=d	0.76
				P					

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0.85

0.91

NS

NS

 $p^* p = 0.004$ p = 0.002

 $^*p = 0.0005$

 $^*p = 0.009$

63.97

0
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Summary of Data

			Total Volumes	nes	S.	Serial Chest tube Hbg	tube Hbg		
	Total volume loss	Total Hgb Loss	Chest tube	Sacrifice	<u>L</u>	0-30min	30-60min	60-120min	120-180min
KPI-1	298	16.58	185	113	J.,,	3.7	4.3	9.8	6.2
KPI-2	266	15.19	198	89	L ,_	4.3	6.4	6.7	5.7
KPI-3	354	20.21	142	212	1	4.1	4.4	7	7.1
KPI-4	258	8.99	190	89	J	2.8	4	4.4	1.9
KPI-5	168	14.63	96	72	l	6.3	6.5	7	6.7
KPI-6	266	15.31	188	78	1	4.1	6.1	5.6	6.3
KPI-7	172	7.7	134	38	L	3.1,	4.6	5.4	4.4
KPI-8	184	10.14	158	26	<u>l</u>	6.9	5.8	5.4	4.2
							!		
MEAN	245.75	13.59		<u>[2</u>	MEAN	4.41	5.26	6.26	5.3
STDEV	66.24	4.26		Ţ <u>V</u>	STDEV	1.45	1.04	1.32	1.72
NS-1A	396	24.95	274	92	 -	7.7	9.8	6.1	5.4
NS-2	342	24.87	236	106	I	7.2	7.4	9.7	7.1
NS-3	294	20.46	252	42	1	5.4	7.5	7.5	6.5
NS-4	385	27.59	303	82	I—-	8.4	7.2	7.1	6.3
NS-5	288	18.23	140	148	<u> </u>	7.5	7.2	5.2	5.6
9-SN	469	31.59	261	208		4	7	7.3	7.4
NS-7	338	23.26	218	120		7.5	7.7	5.8	4.2
NS-8	272	17.96	206	99	,	7.4	8.2	9	5.3
					•				
MEAN	344.25	23.61			MEAN	68.9	7.6	6.58	6.1
	_				1				